Docket No.: 10806-155

PATENT

CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231on **March 24, 2003**.

Lynne W. Moore

Lynne W. Moore

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Appellant:	Barbro Hemmendorff et al	:	Paper No.:
Serial No.:	09/743,023	:	Group Art Unit: 1637
Filed:	March 7, 2001	:	Examiner: Chunduru, Suryaprabha

For: **METHOD FOR THE PRODUCTION OF RECOMBINANT PEPTIDES WITH A LOW AMOUNT OF TRISULFIDES**

APPEAL BRIEF

Box AF
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed by Certificate of Mailing on January 24, 2003 and received by the U.S. Patent and Trademark Office on January 28, 2003.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee of the present application, Pharmacia AB.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellant, the Appellants' undersigned legal representatives or the Assignee which will directly effect or be directly effected by or having a bearing on the Board's decision in the present appeal.

III. STATUS OF THE CLAIMS

Claims 1-3, 5-8 and 11-22 are pending in the present application. Claims 4, 9 and 10 have been cancelled. Claims 1-3, 5-8 and 11-22 stand rejected and are the subject of the present appeal. A complete copy of the pending claims 1-3, 5-8 and 11-22 on appeal is set forth in the Appendix.

IV. STATUS OF AMENDMENTS FILED SUBSEQUENT TO THE FINAL REJECTION OF THE CLAIMS

No amendments to the claims were presented subsequent to the final rejection set forth in the Official Action dated September 24, 2002.

V. SUMMARY OF THE INVENTION

According to independent claim 1, the invention is directed to a method for the production of recombinant peptides with a low amount of trisulfides. The method comprises fermenting cells to produce the recombinant peptides. A metal salt is added during or after the fermentation step, prior to peptide isolation.

Claims 3, 5-8 and 11-12 further define the method of claim 1. According to claim 3, the addition is performed directly after fermentation. According to claim 5, pH is equal to or lower than pH 7. According to claim 6, the metal salt is potassium or sodium salt. According to claim 7, the salt is potassium- or sodium phosphate or acetate. According to claim 8, the peptide is growth hormone. According to claim 11, the metal salt is an alkali metal salt or an alkali earth metal salt. According to claim 12, the peptide is human growth hormone.

According to independent claim 2, the invention is directed to a method for the reduction of the amount of trisulfides in the production of recombinant peptides. The method

comprises fermenting cells to produce recombinant peptides. A metal salt is added during or after fermentation, prior to peptide isolation.

Claims 13-19 further define the method of claim 2. According to claim 13, the addition is performed directly after fermentation. According to claim 14, the metal salt is an alkaline metal salt or an alkali earth metal salt. According to claim 15, pH is equal to or lower than pH 7. According to claim 16, the metal salt is potassium or sodium salt. According to claim 17, the salt is potassium- or sodium phosphate or acetate. According to claim 18, the peptide is growth hormone. According to claim 19, the peptide is human growth hormone.

According to independent claim 20, the invention is directed to a method for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides. The method comprises fermenting cells to produce recombinant peptides. A metal salt is added during or after fermentation, prior to peptide isolation.

According to independent claim 21, the invention is directed to a method for the reduction of the amount of trisulfides in the production of recombinant growth hormone. The method comprises fermenting cells to produce recombinant growth hormone. A metal salt is added during or after the fermentation step, prior to growth hormone isolation.

According to independent claim 22, the invention is directed to a method for the reduction of the amount of trisulfides in the production of recombinant peptides. The method comprises fermenting cells to produce recombinant peptides. A metal salt is added during or after the fermentation step, prior to peptide isolation. The pH during and after fermentation is less than or equal to 7.

The addition of the metal salt during or after fermentation, prior to peptide isolation, provides improved recombinant peptide production by inhibiting the activity of H_2S and thus reducing the formation and amount of modified recombinant peptides comprising an extra sulfur atom (a trisulfide) (page 2, lines 21-30).

VI. ISSUE ON APPEAL

There is one issue on appeal for review by the Board, as follows:

The rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102(e) as being anticipated by Builder et al, U.S. Patent No. 5,663,304.

VII. GROUPING OF THE CLAIMS

With respect to the above-noted issue on appeal, Appellants submit that independent claims 1, 2 and 20-22 are independently patentable. Appellants concede that claims 1, 3, 6-7 and 11 stand or fall together, and claims 2, 13, 16-18 stand or fall together. However, Appellants submit that claims 5, 8 and 12 are independently patentable from claim 1 from which they depend. Appellants also submit that claims 15, 18 and 19 are independently patentable from claim 2 from which they depend. Reasons in support of the independent patentability of these claims are set forth below.

VIII. ARGUMENT

As will be set forth in detail below, the methods defined by claims 1-3, 5-8 and 11-22 are not anticipated by Builder et al, U.S. Patent No. 5,663,304. Accordingly, the rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102(e) should be reversed. Favorable action by the Board is respectfully requested.

A. The Invention

As set forth above, the present invention is directed to methods for the production of recombinant peptides. According to independent claim 1, the method is directed to the production of recombinant peptides with a low amount of trisulfides. The method comprises fermenting cells to produce the recombinant peptides. A metal salt is added during or after the fermentation step, prior to peptide isolation.

According to independent claim 2, the method is directed to the reduction of the amount of trisulfides in the production of recombinant peptides. The method comprises fermenting cells to produce recombinant peptides. A metal salt is added during or after fermentation, prior to peptide isolation.

According to independent claim 20, the method is directed to the reduction in the formation of the amount of trisulfides in the production of recombinant peptides. The method comprises fermenting cells to produce recombinant peptides. A metal salt is added during or after fermentation, prior to peptide isolation.

According to independent claim 21, the method is directed to the reduction of the amount of trisulfides in the production of recombinant growth hormone. The method comprises fermenting cells to produce recombinant growth hormone. A metal salt is added during or after the fermentation step, prior to growth hormone isolation.

According to independent claim 22, the method is directed to the reduction of the amount of trisulfides in the production of recombinant peptide. The method comprises fermenting cells to produce recombinant peptides. A metal salt is added during or after the fermentation step, prior to peptide isolation. The pH during and after fermentation is less than or equal to 7.

The addition of a metal salt during or after fermentation, prior to peptide isolation provides improved recombinant peptide production by inhibiting the activity of H_2S and thus reducing the formation and amount of modified recombinant peptides comprising an extra sulfur atom.

B. The Claimed Methods are Not Anticipated by Builder et al

The methods as defined by claims 1-3, 5-8 and 11-22 are not anticipated by and are patentably distinguishable from Builder et al.

1. The Rejection

The Examiner asserted that Builder et al teach a method for the production of recombinant peptides comprising fermenting cells to produce recombinant peptides in the presence of metal salt prior to peptide isolation. The Examiner also asserted that Builder et al teach that the use of metals facilitates disulfide oxidation of polypeptides and yields correct refolding of the misfolded polypeptide contained in host cells. Finally, the Examiner asserted that the claimed methods and the phrase "the low amount of trisulfides" are inherently disclosed by Builder et al as the reference discloses the use of a special buffer to avoid the possibility of producing polypeptides containing disulfide adducts which favor refolding of the misfolded polypeptide.

2. Builder et al do Not Anticipate the Claimed Methods

Builder et al disclose a method for increasing the yield of correct refolding of a misfolded polypeptide, specifically IGF-I, and reactivating misfolded IGF-I contained in host cells. While Builder et al disclose that metal salts are provided in the IGF-I fermentation medium, Appellants find no teaching or reference for reducing trisulfide formation in the

production of recombinant peptides, as presently claimed. Builder et al only broadly assert that the medium may be "supplemented as necessary" with various components including, among others, salts (see column 15, line 65--column 16, line 12). Appellants find no teaching or reference for using a metal salt for reducing trisulfide formation in the production of recombinant peptides.

Additionally, the Examiner asserted that the limitation in the preamble of the claim is not given patentable weight. However, the Manual Patent Examining Procedure §2111.02 states that "the claim preamble must be read in the context of the entire claim. The determination of whether preamble recitations are structural limitations or mere statements of purpose or use 'can be resolved only on review of the entirety of the [record] to gain an understanding of what the inventors actually invented and intended to encompass by the claims'. *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989)". As disclosed in the specification and recited in the claims, the inventors have invented methods for the production of recombinant peptides with a low amount of trisulfides, methods for the reduction of the amount of trisulfides in the production of recombinant peptides, and a method for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides. It is clear from the entirety of the record that the preamble recites a limitation of the present method claims and thus, should be given patentable weight.

In the Advisory Action of January 23, 2003, the Examiner asserted that the limitation "the low amount of trisulfides" on which Appellants rely does not recite actual values or concentration of the low amounts of trisulfides and thus, Builder et al inherently teaches this limitation. However, Appellants note that the phrase "the low amount of trisulfides" is not

recited in claims 2 and 13-22, and thus this assertion by the Examiner is inapplicable to claims 2 and 13-22.

Moreover, the presently claimed methods are not inherent in the teachings of Builder et al. Builder et al teach the facilitation of disulfide oxidation of polypeptides to promote refolding and correct disulfide bonding in a misfolded polypeptide. In contrast, the present invention teaches the reduction of trisulfide bond formation by the inhibition of H_2S activity. The Examiner asserted that the claimed methods are inherently disclosed by Builder et al as the reference discloses the use of a special buffer to avoid the possibility of producing polypeptides containing disulfide adducts. However, a disulfide adduct, as disclosed in Builder et al, is the product of the interaction between a protein and a reducing agent, such as glutathione, and thus, a disulfide adduct does not "inherently comprise" trisulfide bonds as the Examiner appears to assert. Further, as acknowledged by the Examiner, Insulin-Like Growth Factor (IGF-I) is not known to produce trisulfides when the polypeptide is formed. Thus, Builder et al cannot inherently teach the present methods of reducing trisulfide amount or formation. Finally, as Builder et al fail to provide a specific teaching in the Examples of the production of a peptide, such as growth hormone, which involves trisulfide formation, the methods presently claimed are not inherent in the teachings of Builder et al.

"Anticipation requires that every limitation of the claim in issue be disclosed, either expressly or under principles of inherency, in a single prior art reference", *Corning Glass Works v. Sumitomo Electric U.S.A. Inc.*, supra, at 1965 (Fed.Cir. 1989), *citing Kalman v. Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983), *cert. denied*, 224 USPQ 520 (1984). Inherency may not be established by "probabilities or possibilities", *Scaltech, Inc. v. Retec/Tetra, LLC.*, 51 USPQ2d 1055, 1059 (Fed. Cir. 1999). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient", *In re Oelrich*, 212

USPQ 323, 326 (CCPA 1981). In view of the failure of Builder et al to disclose methods for the production of recombinant peptides with a low amount of trisulfides, methods for the reduction of the amount of trisulfides in the production of recombination peptides or in the production of recombinant growth hormone, or methods for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides as defined by the claims, Builder et al do not disclose each element of the claims under consideration and therefore does not support a rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102. The rejection should therefore be reversed.

3. Claims 5 and 15 are Independently Patentable

Claim 5 recites a method according to claim 1, wherein pH is equal to or lower than pH 7. Claim 15 recites a method according to claim 2, wherein the pH is equal to or lower than pH 7. Appellants find no teaching or reference in Builder et al of a method for the production of recombinant peptides with a low amount of trisulfides comprising fermenting cells to produce the recombinant peptides, wherein a metal salt is added during or after the fermentation step, prior to peptide isolation as recited in claim 1, and wherein pH is equal to or lower than pH 7 as recited in claim 5. Appellants also find no teaching or reference in Builder et al of a method for the for the reduction of the amount of trisulfides in the production of recombinant peptides comprising fermenting cells to produce the recombinant peptides, wherein a metal salt is added during or after the fermentation step, prior to peptide isolation as recited in claim 2, and wherein pH is equal to or lower than pH 7 as recited in claim 15. Rather, Builder et al teach that the peptide fermentation process is performed at a pH of 7.1-7.5 (see Example 1C).

The assertion by the Examiner that Builder et al disclose at column 28, lines 5-33 that the pH during or after the fermentation step was less than or equal to 7 and thus renders the claims anticipated is not accurate. The steps disclosed in Builder et al at column 28, lines 5-33 include steps which are after fermentation but are during and after peptide isolation. Specifically, the step of precipitating the peptide, disclosed at column 28, lines 5-11, is the step which isolates the peptide. The step of refolding the peptide, disclosed at column 28, lines 12-33, is performed after the peptide is isolated by the precipitation step. Additionally, as noted above, Builder et al teach in Example 1C that the fermentation process is performed at a pH of 7.1-7.5. Therefore, Builder et al does not teach or suggest the methods as defined by the present claims, as the presently claimed methods recite that the pH is equal to or lower than pH 7 during or after fermentation, but prior to peptide isolation.

"Anticipation requires that every limitation of the claim at issue be disclosed, either expressly or under principles of inherency, in a single prior art reference", *Corning Glass Works, supra.* In view of the failure of Builder et al to disclose, either expressly or under principles of inherency, the methods as recited in the claims 5 and 15, Builder et al do not disclose each element of the present claims and therefore do not anticipate claims 5 and 15 under 35 U.S.C. §102(e). The rejection should therefore be reversed.

4. Claims 8, 12, and 18-19 are Independently Patentable

Claim 8 recites a method according to claim 1, wherein the peptide is growth hormone. Claim 12 recites a method according to claim 1, wherein the peptide is human growth hormone. Claim 18 recites a method according to claim 2, wherein the peptide is growth hormone. Claim 19 recites a method according to claim 2, wherein the peptide is human growth hormone.

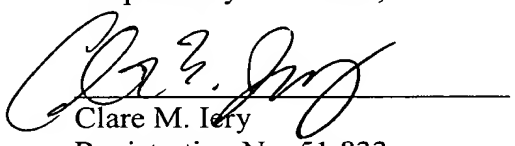
Appellants find no teaching or reference in Builder et al of a method for the production of recombinant peptides with a low amount of trisulfides comprising fermenting cells to produce the recombinant peptides, wherein a metal salt is added during or after the fermentation step, prior to peptide isolation as recited in claim 1, and wherein the peptide is growth hormone (claim 8) or human growth hormone (claim 12). Appellants also find no teaching or reference in Builder et al of a method for the reduction of the amount of trisulfides in the production of recombinant peptides comprising fermenting cells to produce the recombinant peptides, wherein a metal salt is added during or after the fermentation step, prior to peptide isolation as recited in claim 2, and wherein the peptide is growth hormone (claim 18) or human growth hormone (claim 19). Rather, as noted in detail above, Builder et al fail to provide a specific teaching in the examples of the production of a peptide, such as growth hormone, which involves trisulfide formation. Moreover, IGF-I, the peptide to which Builder et al specifically refer, and exemplify, is not known, as acknowledged by the Examiner, to produce trisulfides when the polypeptide is formed.

"Anticipation requires that every limitation of the claim at issue be disclosed either expressly or under the principles of inherency in a single prior art reference", *Corning Glass Works, supra.* Inherency may not be established by "probabilities or possibilities", *Scaltech Inc., supra.* "The mere fact that a certain thing may result from a given set of circumstances is not sufficient", *In re Oelrich, supra.* In view of the failure of Builder et al to disclose either expressly or under the principles of inherency, the methods as defined by claims 8, 12 18 or 19, Builder et al do not disclose each element of the present claims and therefore not anticipate claims 8, 12, 18 and 19 under 35 U.S.C. §102(e). This rejection should therefore be reversed.

IX. CONCLUSIONS

For the reasons set forth in detail above, the methods defined by claims 1-3, 5-8 and 11-22 are not anticipated by and are patentably distinguishable from Builder et al. Accordingly, the rejection of claims 1-3, 5-8 and 11-22 under 35 U.S.C. §102(e) should be reversed. Favorably action by the Board is respectfully requested.

Respectfully submitted,



Clare M. Iery
Registration No. 51,833
Dinsmore & Shohl LLP
1900 Chemed Center
255 East Fifth Street
Cincinnati, Ohio 45202
(513) 977-8192

875028

APPENDIX

1. Method for the production of recombinant peptides with a low amount of trisulfides, comprising fermenting cells to produce the recombinant peptides, wherein a metal salt is added during or after the fermentation step, prior to peptide isolation.

2. Method for the reduction of the amount of trisulfides in the production of recombinant peptides comprising fermenting cells to produce recombinant peptides, wherein a metal salt is added during or after fermentation, prior to peptide isolation.

3. Method according to claim 1, wherein the addition is performed directly after fermentation.

5. Method according to claim 1, wherein pH is equal to or lower than pH 7.

6. Method according to claim 1, wherein the metal salt is potassium or sodium salt.

7. Method according to claim 6, in which the salt is potassium- or sodium phosphate or acetate.

8. Method according to claim 1, wherein the peptide is growth hormone.

11. Method according to claim 1, wherein the metal salt is an alkali metal salt or an alkali earth metal salt.

12. Method according to claim 1, wherein the peptide is human growth hormone.

13. Method according to claim 2, wherein the addition is performed directly after fermentation.

14. Method according to claim 2, wherein the metal salt is an alkali metal salt or an alkali earth metal salt.

15. Method according to claim 2, wherein pH is equal to or lower than pH 7.

16. Method according to claim 2, wherein the metal salt is potassium or sodium salt.

17. Method according to claim 16 in which the salt is potassium- or sodium phosphate or acetate.

18. Method according to claim 2, wherein the peptide is growth hormone.

19. Method according to claim 2, wherein the peptide is human growth hormone.

20. Method for the reduction in the formation of the amount of trisulfides in the production of recombinant peptides, comprising fermenting cells to produce recombinant peptides, wherein a metal salt is added during or after fermentation, prior to peptide isolation.

21. Method for the reduction of the amount of trisulfides in the production of recombinant growth hormone, comprising fermenting cells to produce recombinant growth hormone, wherein a metal salt is added during or after the fermentation step, prior to growth hormone isolation.

22. Method for the reduction of the amount of trisulfides in the production of recombinant peptides, comprising fermenting cells to produce recombinant peptides, wherein a metal salt is added during or after the fermentation step prior to peptide isolation, and wherein the pH during and after fermentation is less than or equal to 7.